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ADDRESSING RESPIRATORY DISCOMFORT IN THE VENTILATED PATIENT

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Although respiratory discomfort (dyspnea) is as common as pain in seriously ill patients,[1] there is no formal requirement to assess and manage it, such as the "fifth vital sign" requirement for pain assessment and management.

Mechanical ventilation is the most frequently used life-support measure in the intensive care unit (ICU). It is also used during anesthesia and the initial phase of postanesthesia awakening, and at home in patients with chronic respiratory failure. Many patients who are mechanically ventilated are thus conscious (or even fully awake), yet they can experience rapid and important changes in their respiratory status and metabolic needs. It is thus not surprising that ventilated patients do experience respiratory discomfort. They can report and quantify it, and there are strategies to address it. In this chapter we (a) propose that respiratory discomfort be routinely assessed in ventilated patients, and (b) suggest some approaches to managing this discomfort with minimal sedation. Together, these could be termed *patient-centered ventilation*.[2] There is, however, a paucity of studies directly addressing prevalence, outcomes, and mechanisms of dyspnea and its relief in acutely ventilated patients.

OCCURRENCE AND SEQUELAE OF RESPIRATORY DISCOMFORT IN VENTILATED PATIENTS

Although we lack large-scale studies on the prevalence of dyspnea in mechanical ventilation, there have been a few studies in which a small sample of acutely ventilated patients have been asked to rate dyspnea.[3–8] In three studies the severity of dyspnea was stratified: In a combined total of 204 patients, 19% of the respondents reported moderate to severe discomfort.[3,6,7] In one study, patients were asked to characterize the quality of their discomfort: 69% reported experiencing air hunger; 51% reported excessive work/effort. About a third of the foregoing patients experienced both air hunger and work/effort.[7] In another study, 29% of ventilated patients recalled after their stay in the ICU that

they had been moderately to extremely bothered by not getting enough air from the endotracheal tube, which we equate to air hunger.[9] Many patients, however, were too heavily sedated to respond; many of these latter patients had probably been heavily sedated in an attempt to alleviate respiratory discomfort. This clearly indicates that there is a problem to address. As discussed below, heavy sedation is not necessarily an adequate solution and may be harmful.

There is a clear association between anxiety and dyspnea in patients.[10–12] In laboratory subjects, experimentally induced air hunger produces more discomfort and more anxiety than tasks that require a great deal of respiratory work and effort.[13] In critically ill patients, emotional reactions such as panic, anxiety, and fear are significantly correlated with patient–ventilator dyssynchrony.[14] Dyspnea can cause anxiety, even in healthy subjects who experience dyspnea in a safe laboratory situation.[13,15,16] Conversely, anxiety can cause dyspnea. This is true even in the absence of cardiopulmonary pathology; for example, dyspnea is the most common symptom in anxiety and panic disorders.[17] Because of this reciprocal causation, the possibility of positive feedback exists in ventilated patients, with dyspnea causing anxiety, which then exacerbates the dyspnea. In a series of mechanically ventilated patients reporting dyspnea, multivariate analysis showed that the strongest statistical association with respiratory discomfort was with anxiety.[7] In the subset of these patients whose dyspnea was lessened by changes in ventilator settings, anxiety was also reduced, suggesting that the dyspnea caused the anxiety.

Survivors of mechanical ventilation in the ICU often carry surprisingly dark recollections of the experience. A recent study reported that 15% of patients recalled feeling at risk of being murdered, 17% felt betrayed, 39% felt at risk of imminent death, and 55% felt they were being suffocated.[18] Thus, it should not be surprising that posttraumatic stress disorder (PTSD) is now recognized as a common sequela of ICU experience.[18–21] PTSD symptom scores in the post-ICU population are significantly correlated with duration of mechanical ventilation,[19] and with recalled memories of respiratory distress.[20] A number of reasons for these connections can be postulated, but the possibility cannot be ignored that inescapable dyspnea is one of the traumatizing events leading to PTSD in this population.

ASSESSMENT OF DISCOMFORT IN THE VENTILATED PATIENT

Ask the Patient

The first step in addressing dyspnea is to determine how much and what kind of discomfort the patient is experiencing. A full assessment requires that the patient be alert enough to respond to simple direct questions regarding the intensity and quality of discomfort. In heavily sedated patients, the daily wake-up practiced in many ICUs[22] provides an opportunity to assess the intensity of dyspnea and attempt to reduce it with nonpharmacologic approaches before evaluating the need for further sedation.

TABLE 55-1: SAMPLE PATIENT ASSESSMENT QUESTIONNAIRE

Please indicate on this 10-point scale how your breathing feels:
10 EXTREMELY SHORT OF BREATH
9
8
7
6
5
4
3
2
1
0 BREATHING IS COMFORTABLE
Which of the following phrases describes the way you feel?
1. Not getting enough air (if yes, ask a and b and skip 2; if no, ask 2)
   a. Breaths are not deep enough
   b. Breaths are not fast enough
2. Getting too much air (if yes, ask a and b)
   a. Breaths are too deep
   b. Breaths are too fast
3. Too much effort to breathe
4. Chest feels tight or constricted

Several rating methods have been shown to be feasible in intubated and ventilated patients. Patients who are alert enough to respond but who cannot speak can provide information through simple number, word, or visual analog scales, similar to those routinely used in clinical pain assessment.[3,5,23] Patients can point to the appropriate responses but in some cases the interviewer will need to say or point to responses in succession and stop when the patient indicates with a blink or other sign. The intensity scale may be combined ad hoc with a list of descriptors from which the subject can choose; descriptor lists often make the process easier for patients who find it difficult to describe unfamiliar internal sensations.[24] Table 55-1 shows a brief sample assessment procedure. More extensive and sophisticated assessment may be required for research purposes.[25]

Physical Signs May Correlate Poorly with Discomfort Level

Many caregivers rely on physical signs such as respiratory rate, heart rate, use of accessory muscles, synchrony with mechanical ventilation, diaphoresis, and facial expression. Recently, a systematized Respiratory Distress Observation Scale (RDOS) was developed and validated in spontaneously breathing subjects.[26] This scale comprises measures of heart rate, respiratory rate, accessory muscle use, paradoxical breathing pattern, restlessness, grunting at end-expiration, nasal flaring, and fearful facial display. Some of these signs are likely to be altered by mechanical

ventilation, so adaptation and validation of the scale for ventilated patients is needed. Signs can be very useful when patients are unable to communicate, but they can be misleading.[5] Patients vary widely in their behavioral responses to discomfort; thus, as with pain, physical signs may overestimate or underestimate the degree of discomfort, and they give little information regarding its cause. Reliance on inconsistent physical signs was also a problem in pain assessment until accrediting organizations, such as Joint Commission on Accreditation of Healthcare Organizations (JCAHO), began to require more direct assessment and management of pain.[27] Caregivers should ask the patient whenever feasible.

Dyssynchrony of patient and ventilator is associated with discomfort. It has been suggested that it is a cause of discomfort and conversely that it is a result of discomfort (both may be true). The interaction between modern ventilators and patients is a result of the interface between two complex control systems, and the resulting pressure and flow waveforms can be complex. Dyssynchrony is usually assessed qualitatively by visual inspection of waveforms, but some investigators are attempting to formally quantify dyssynchrony.[28] When such methods have matured, they must be validated against subjective reports of patients. Again, we emphasize that when patients can report their discomfort, their reports should be weighed more heavily than physical signs. To date, the available studies of patient–ventilator synchrony have not measured its relationship to respiratory discomfort.

NEUROPHYSIOLOGIC SURROGATES OF DYSPNEA

There are a number of circumstances under which a ventilated patient will be unable to communicate verbally with caregivers and where physical signs of respiratory distress will be difficult to interpret. A particularly difficult instance is the patient paralyzed with neuromuscular blockers. Neurophysiologic surrogates of dyspnea would be particularly useful in this setting. Although in theory one might be able to assess respiratory discomfort using functional magnetic resonance imaging of the brain,[29] this is unlikely to become practical for clinical use in the foreseeable future.

Electroencephalography, however, may provide a more practical method. In normal volunteers under experimental conditions, preinspiratory potentials become apparent during noninvasive mechanical ventilation when respiratory discomfort is induced through the use of inappropriate ventilator settings.[30] Preliminary observations in mechanically ventilated patients suggest that similar monitoring of respiratory-related electroencephalography activity could help detect respiratory discomfort in noncommunicant patients. This approach would allow a continuous surveillance that would be particularly useful in patients liable to experience frequent changes in respiratory status. The clinical utility of these techniques and the spectrum of their applicability are important research targets.

In addition, assessing the electromyographic activity of inspiratory muscles can be useful as a measure of respiratory drive, one of the determinants of respiratory sensation discussed in the air hunger section. There is experimental and clinical evidence that "ventilator fighting" or patient–ventilator dyssynchrony can be associated with visibly increased activity of inspiratory neck muscles, parasternal intercostals, and upper airway dilators including the tongue.[31–33] Correlations between respiratory muscle activity and dyspnea have been observed.[31,33] The clinical usefulness of respiratory muscle electromyography to assess and monitor respiratory discomfort is another likely research topic.

Discomfort Can Be Caused by Dyspnea Combined with Other Sensations

A particular patient's discomfort may be caused by a mix of respiratory discomfort and nonrespiratory sensations, such as pain and nausea. Little is known about how these sum into total discomfort; in some cases, one noxious stimulus can occlude perception of another. The limited data available suggest that simultaneous dyspnea and pain can be separately scaled, and that the presence of one does not strongly affect the other, at least under controlled circumstances.[34] Sensations of respiratory discomfort other than dyspnea (e.g., secondary to cough or irritation from the endotracheal tube) may also be present. Different forms of dyspnea such as air hunger and excessive work of breathing may be simultaneously present, and are thought to be additive.[35] The problems of ventilated patients are therefore varied and complex; there is no single approach that will work in all patients.

PRIMER ON DYSPNEA

Different Forms of Dyspnea

Several different mechanisms give rise to respiratory discomfort; the mechanism(s) operating in an individual patient will guide the treatment approach selected. The quality of discomfort is one guide to understanding which mechanisms are in play; other clues come from physical examination and measurement of ventilatory variables (see "Approach to the Ventilated Patient with Dyspnea" below). There are at least three distinct qualities of uncomfortable breathing sensations: *air hunger, effort* or *work,* and *tightness.* These different forms of dyspnea are caused by different afferent mechanisms and are evoked by different physiologic stimuli.

Theories developed in the late 1960s and early 1970s attributed all dyspnea to excessive work or effort of breathing.[36] Although work of breathing has since been disproved as the sole origin of dyspnea,[37–39] this model still dominates thinking in the realm of clinical mechanical ventilation.[40,41] Attempts to understand a patient's discomfort based only on work of breathing will not be fully effective; in fact, extremely unpleasant dyspnea can be evoked in the absence of any respiratory work.

AIR HUNGER

Air hunger is the conscious perception of the need for more air that is typically described by subjects as "not getting enough air," "uncomfortable urge to breathe." This is the sensation felt by normal subjects at the end of a long breathhold.[15,38] Subjects comment that air hunger is a threatening or frightening sensation. Healthy subjects exposed briefly to air hunger in our laboratory have reported that "it's a feeling…you're going to die because you're not getting enough air." Even moderate air hunger is highly aversive if prolonged, with one subject commenting that "if I felt I had to live my life feeling like that I would jump out the window [commit suicide]." Quotes from patients with dyspnea can be remarkably similar: "When the shortness of breath was at its extreme I thought I was going to die," and "…wouldn't want to live if it continued."[42]

Air hunger arises from stimulation of arterial chemoreceptors and from other drives to breathe; a rise in partial pressure of arterial carbon dioxide (Pa_{CO_2}) or a fall in partial pressure of arterial oxygen (Pa_{O_2}) will evoke air hunger.[37,43–46] Air hunger is not caused by contraction of respiratory muscles; complete respiratory paralysis does not abolish or even diminish the air hunger response to CO_2.[37–39] It is hypothesized that air hunger is transmitted to the cerebral cortex by a corollary discharge of medullary respiratory center activity (also known as *ventilatory drive*). Such a corollary discharge has been described in the midbrain and thalamus of decorticate cats, presumably en route to the cortex.[47–49] Although air hunger is stimulated by medullary drive, the two are not equivalent; other processes modify the translation of drive into the perception of air hunger in the cerebral cortex. Air hunger is associated with activation of the paralimbic cortex in humans, a region of the brain long associated with emotional responses and learning. The principal activation reported in studies of experimental dyspnea is the anterior insula, with stronger activations on the right than on the left (Fig. 55-1A and B). The anterior insula is activated by several other unpleasant sensations that provide information on primal biologic drives, such as pain, thirst, and hunger.[29,50,51] Air hunger also activates the amygdala, which is implicated in the perception of fear and anxiety (Fig. 55-1C and D).

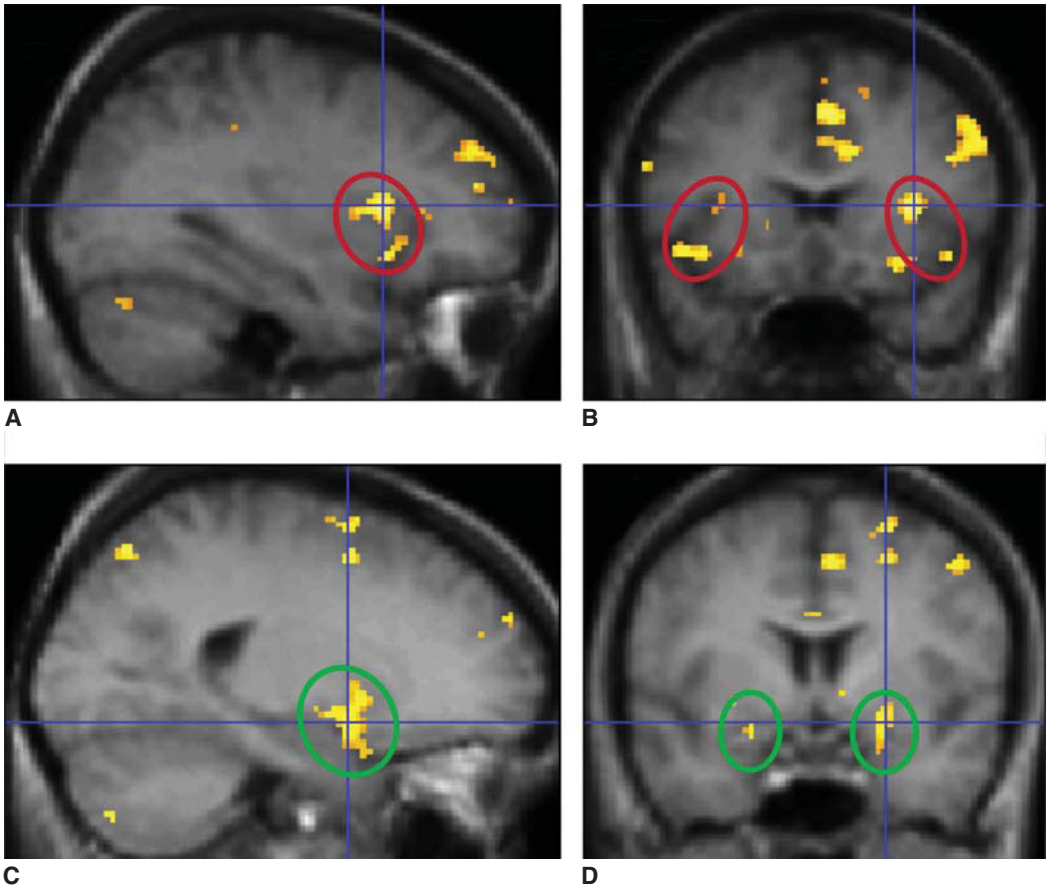

FIGURE 55-1 Functional brain images showing some important paralimbic activations during laboratory-induced air hunger (data from Evans et al[29]). Air hunger was induced during volume-control ventilation by lowering tidal volume (V_T); *red ovals* in *A* and *B* indicate activations in the anterior insular cortex (IC). The sagittal section (**A**) is in the right hemisphere, 34 mm from the midline; the coronal section (**B**) is 16 mm forward of the anterior commissure. The anterior insula is also involved in hunger, thirst, and pain. *Green ovals* in *C* and *D* indicate activations in the amygdala. The sagittal section (**C**) is in the right hemisphere, 24 mm from the midline; the coronal section (**D**) is 4 mm forward of the anterior commissure. The amygdala is implicated in states of fear and anxiety. These images were obtained using blood oxygen level dependent functional magnetic resonance imaging. All activations shown were statistically significant after correction for multiple comparison.

EFFECT OF BLOOD GASES ON AIR HUNGER

There is a substantial amount of information on the interaction of blood-gas levels, level of minute ventilation, and air hunger during mechanical ventilation in normal subjects and in patients who are ventilator-dependent secondary to neuromuscular paralysis. In a study of sixteen healthy subjects ventilated at 10 L/min, end-tidal carbon dioxide tension ($P_{ET}CO_2$) was raised by increasing inspired CO_2. An increase of 10 torr produced a level of respiratory discomfort that subjects could not tolerate even for a few minutes (Fig. 55-2).[15] This occurred despite a background of high oxygen and with minute ventilation ($\dot{V}_E$) greater than 150% of the normal resting level. In practical terms, this implies that modest acute increases in partial pressure of carbon dioxide (P_{CO_2}) that may seem clinically unimportant can be a source of profound discomfort.

An acute rise in Pa_{CO_2} evokes severely uncomfortable air hunger during volume-control ventilation in both healthy subjects and in alert patients ventilated for respiratory muscle paralysis.[23,38,39] The sensations of air hunger and work/effort produced by mild hypercapnia in spontaneously breathing healthy subjects are increased by partial neuromuscular block, even at $P_{ET}CO_2$ and $\dot{V}_E$ levels similar to those present before the block.[52,53] This may explain why exertional dyspnea occurs in patients with profound neuromuscular weakness.

How do responses to chronically altered blood gases compare to the acute stimulus–response relationships for air hunger detailed above (which were obtained in exposures of 10 minutes or less)? Common clinical experience leads to the hypothesis that there is adaptation to chronic changes in blood gases; for instance, the common observation that some patients with chronic obstructive pulmonary disease do not report dyspnea at resting P_{CO_2} in excess of 50 torr, a level that is intolerable to normal subjects at comparable ventilation levels. A direct test of the hypothesis was obtained in mechanically ventilated patients who adapted to a gradual 15-torr rise in Pa_{CO_2} produced by slowly raising inspired P_{CO_2} while holding ventilation and partial pressure of arterial oxygen (Pa_{O_2}) constant.[23] The air hunger response to acute hypercapnia was tested before and after the adaptation period. Within 2 to 3 days, the acute response to hypercapnia had also shifted by 15 torr, essentially complete adaptation (Fig. 55-3). The authors attributed this shift to neural adaptation, rather than acid–base compensation; thus, it may apply to other stimuli such as hypoxia.

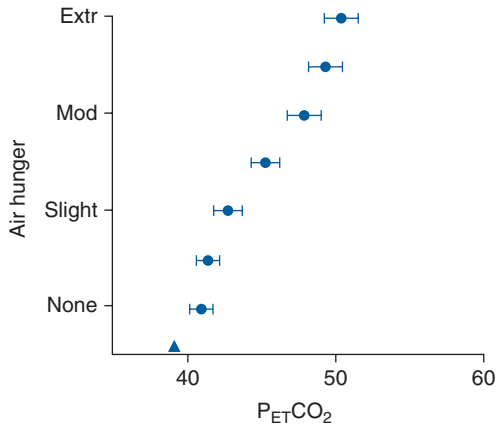

FIGURE 55-2 Air hunger response to an acute rise in end-tidal carbon dioxide tension ($P_{ET}CO_2$) produced by inspired CO_2 in normal healthy men and women (*closed circles*). The prevailing chronic level of $P_{ET}CO_2$ is indicated by *a triangle*. *Bars* indicate standard error of the mean. Volume-control ventilation was delivered via a mouthpiece at 0.16 L · min^{-1} · kg^{-1}. Subjects in these experiments were instructed to rate "discomfort due to your urge to breathe." "Extreme" (*Extr*) on the rating scale was defined to the subjects as an intolerable level, and "moderate" (*Mod*) was defined as a level that could be tolerated for several minutes. (Data were replotted from Banzett et al.[15])

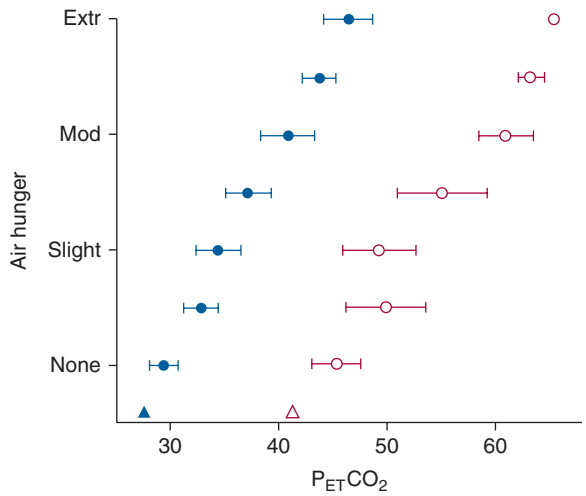

FIGURE 55-3 Adaptation of air hunger response to prevailing chronic level of $P_{ET}CO_2$ (*triangles*) in four ventilator-dependent patients. Response to acute hypercapnia (*circles*) is shown at baseline chronic level of $P_{ET}CO_2$ (*filled symbols*; mean of 27 torr in these chronically overventilated patients), and after adaptation for several days to a mean $P_{ET}CO_2$ of 41 torr (*open symbols*). Bars indicate standard error of the mean. The increase in chronic partial pressure of carbon dioxide (P_{CO_2}) was effected by adding inspired CO_2 at the same minute ventilation ($\dot{V}_E$). (Data replotted from Bloch-Salisbury et al.[23])

Subjects report little or no difference between the quality of air hunger evoked by hypoxia versus that evoked by hypercapnia.[46] If P_{CO_2} and ventilation are near normal, pronounced hypoxia is required to evoke air hunger; in healthy subjects an arterial partial pressure of oxygen (P_{O_2}) of 40 to 50 torr produces only mild air hunger if Pa_{CO_2} remains at eucapnic levels.[46] The effects of hypoxia are enhanced by hypercapnia.

EFFECT OF LUNG INFLATION ON AIR HUNGER

Mechanoreceptor input arising from breathing can dramatically reduce air hunger, as demonstrated by the classic experiment in which subjects held their breath until breakpoint and then breathed from a bag containing gas with alveolar concentrations of CO_2 and O_2, preventing improvement of arterial

blood gases.[16,54] Subjects reported immediate relief and could even continue with another breathhold. This phenomenon is manifested during mechanical ventilation as a decrease in dyspnea when tidal volume is increased, as was initially shown in polio patients.[55] Subsequently, mechanoreceptor relief of air hunger has been shown in normal subjects.[29,50,56] Studies of healthy subjects on volume-control ventilation, who have been initially made uncomfortable with mildly elevated P_{CO_2}, show that there is a decline in discomfort (air hunger) as $\dot{V}_E$ is increased with constant blood-gas levels (the solid line in Fig. 55-4). In these subjects, zero discomfort can be achieved, and further increases have no effect, or produce a different form of discomfort, "too much pressure." In normal subjects, the relationship between ventilation and air hunger is linear (A.P. Binks, personal communication). This relief is undiminished in C1–C2 quadriplegic patients who have no motor or sensory innervation of the rib cage and diaphragm, showing that pulmonary stretch receptors that send impulses via the vagus nerve, are able to produce the full response[57] (*dotted line* in Fig. 55-4). It is not clear, however, whether chest wall receptors form a fully redundant pathway capable of providing relief. Tidal volume provided somewhat less relief in double-lung transplant patients than in normal subjects;[56] however, even the diminished response present in these transplant patients may have been caused by reinnervation of the transplanted lung, because the patients were studied 1 to 9 years posttransplantation.[58]

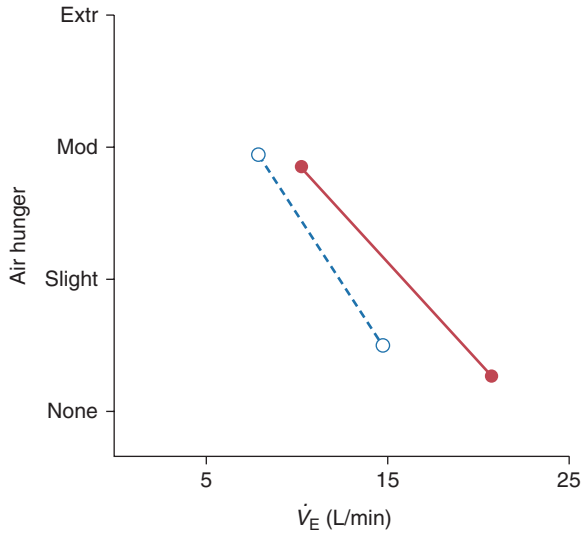

FIGURE 55-4 Relief of air hunger by increased minute ventilation at constant $P_{ET}CO_2$ in normal subjects (*solid line, closed symbols*) and patients with high cervical quadriplegia (*dotted line, open symbols*). In all cases, air hunger was generated by adding inspired CO_2 to increase $P_{ET}CO_2$ above the subjects' baseline $P_{ET}CO_2$. (Mean $P_{ET}CO_2$ in normal subjects was 44 torr and in quadriplegic patients, 34 torr, owing to their lower baseline P_{CO_2}.) $P_{ET}CO_2$ and respiratory frequency were held constant as ventilator tidal volume was varied. (Data for normal subjects combined from Harty et al[56] and Banzett et al[50]; data for quadriplegic patients combined from Manning et al[57] and Bloch-Salisbury et al.[90])

WORK OR EFFORT OF BREATHING

The sense of breathing work or effort arises both from muscle receptors and from corollary discharge arising from cerebral motor cortex activation during volitional respiratory efforts.[59] (Corollary discharge from medullary respiratory centers probably does not give rise to increased work or effort of breathing.) Although some studies of well-trained subjects have shown a distinction between effort and work, most normal subjects and patients do not distinguish the two; thus, we use work/effort to denote the sensation. Work/effort of breathing is perceived when the physical work of breathing is increased by loading the respiratory muscles with high $\dot{V}_E$ or increased impedance, or when increased cortical motor drive is necessitated by respiratory muscle weakness.[53,60–62] Breathing at high lung volume both weakens the muscles (by placing them at a disadvantageous point in the length–tension curve) and loads them by increasing preload and system elastance; this is thought to be an important source of dyspnea in obstructive pulmonary disease.[63–65] In normal subjects, high levels of respiratory work/effort unaccompanied by blood-gas derangements are not as unpleasant or threatening as air hunger.[13,60,62]

In theory, the ventilated patient need not do any respiratory work; ventilators have ample power to assume all work of breathing. Two sources of work, however, commonly arise in ventilated patients. The first we term *wasted work* (i.e., work that does not result in air movement); this includes respiratory efforts that are ineffective because they are out of synchrony with the ventilator, or efforts (although in synchrony) that do not alter airflow (e.g., inspiratory efforts during volume-control inspirations). The second, *productive work,* is performed to lower airway pressure to trigger inspiration during assist control, or to trigger and prolong inspiratory flow during pressure support. Some respiratory work may prevent deconditioning of respiratory muscles.[66,67] Even productive work, however, may be excessive, if for instance the trigger pressure or flow thresholds are set too high especially in the face of high respiratory impedance or respiratory muscle dysfunction. Dynamic hyperinflation (intrinsic positive end-expiratory pressure [PEEP]) is a typical cause of excessive work; in this case the patient must generate inspiratory muscle pressure to overcome the difference between ventilator PEEP and intrinsic PEEP before the ventilator can be triggered. In addition, dynamic hyperinflation is associated with elastic loading caused by flattening of the respiratory system pressure-volume relationship at high lung volumes, and with decreased inspiratory muscle effectiveness secondary to sarcomere shortening and geometry changes. Thus, the effort required to trigger the ventilator and sustain flow above the cutoff level can give rise to excessive work/effort at a time where muscle output is diminished. Depending on the ventilator setting, it can also cause inadequate ventilation, giving rise to air hunger. It is thus likely that dynamic hyperinflation can give rise to a mixed respiratory discomfort combining air hunger and an excessive work/effort.

DYSPNEA ARISING FROM PULMONARY AFFERENTS

There are several diseases in which dyspnea seems to arise from derangements of pulmonary afferent traffic; less is known about the neurophysiology of these forms of dyspnea. *Tightness* arises during bronchoconstriction.[68,69] Tightness is undiminished by mechanical ventilation, and preliminary evidence suggests that it is present during bronchoconstriction in quadriplegic patients with denervated chest walls, suggesting that it arises from pulmonary afferents.[70,71] Pulmonary embolism, pulmonary hypertension, and congestive heart failure all give rise to dyspnea that is disproportional to blood-gas changes or to increased work of breathing. All directly impinge on the lung or its vasculature. It has thus been speculated that these conditions give rise to dyspnea via pulmonary receptors, and there is some evidence implicating vagal afferents, perhaps unmyelinated J-receptors.[72–74]

APPROACH TO THE VENTILATED PATIENT WITH DYSPNEA

If the ventilated patient is experiencing dyspnea, steps should be taken to establish the reason for the dyspnea and corrective measures should be attempted. It may be useful to establish a routine protocol to suit the needs of the unit. If diagnosis and corrective measures are expected to take more than a few minutes, interim relief can usually be obtained by increasing the level of ventilator support. Sedation should be used as a last resort because of the related risks. There are several avenues to pursue before resorting to sedation: assess and remedy problems with obstructed airways, a stiff respiratory system, or weak respiratory muscles; improve ventilator settings; and address neuropsychiatric problems.

Essential information can be obtained from the physical examination (e.g., onset of wheezing, absence of breath sounds, new crackles, use of accessory muscles of ventilation, or pulsus paradoxus) and by measuring airways resistance (Raw), intrinsic PEEP, spontaneous and ventilator-assisted tidal volume, maximal inspiratory and expiratory pressures, and compliance of the respiratory system (sometimes with the use of an esophageal balloon-catheter system to obtain compliance of the lung and chest wall separately).

Reduce Respiratory Drive

Respiratory drive in excess of achieved ventilation is the cause of air hunger, the most common respiratory discomfort reported by mechanically ventilated patients.[7] The most straightforward way to address air hunger is to increase ventilation. When it is not possible or not advisable to increase achieved ventilation, other steps should be taken to reduce drive. Factors such as acidosis, hypoxia, hyperthermia, and anemia should be corrected.[75] Although patients may adapt to hypercapnia over the course of several days, acute increases in Pa_{CO_2} of only a few torr can cause substantial discomfort.[23] When addressing acidosis, it may be possible to use buffers such as tris-hydroxymethyl aminomethane (THAM) that do not increase P_{CO_2}.[76–78]

Correct Increased Respiratory Impedance

Increased resistive or elastic impedance may give rise to air hunger in the ventilated patient by reducing ventilation, either by causing patient triggering efforts to fail, or by reducing tidal volumes delivered by pressure-targeted ventilators. Increased impedance may also give rise to a sense of excessive effort by increasing both wasted and productive work.

EXCESSIVE RESISTANCE

Airways obstruction in ventilated patients as reflected by Raw greater than 10 cm H_2O/L/s is a frequent cause of dyspnea. Table 55-2 lists common causes of high Raw.

In addition to resistance and compliance measures, the pressure and flow waveforms from the ventilator can provide useful diagnostic clues: A sawtoothed pattern is usually caused by retained secretions or condensed water in the expiratory line. Interruption of exhalation by a new inhalation before flow reaches zero indicates the presence of intrinsic PEEP, the magnitude of which should then be measured. Intrinsic PEEP secondary to flow limitation can be distinguished by pressing on the patient's abdomen during expiration. If there is flow limitation, the expiratory waveform will not change. Many of the causes of high Raw listed in Table 55-2 can be identified easily by bronchoscopy. In other instances, the quality of dyspnea reported by the patient can provide important diagnostic clues. For example, our experience is that when bronchoconstriction is the cause, patients complain of chest tightness, whereas other causes of obstruction are usually associated with a sense of increased effort or work to breathe.

The goal is to reduce or eliminate excessive Raw if possible, for instance by suctioning, replacement of the obstructed endotracheal or tracheostomy tube, administration of

TABLE 55-2: COMMON CAUSES OF HIGH AIRWAY RESISTANCE

- Bronchoconstriction
- Inspissated debris in the endotracheal or tracheostomy tube
- Retained secretions in the trachea or bronchi
- Obstruction of the orifice of the endotracheal or tracheostomy tube by the posterior membranous sheath of the trachea secondary to tracheomalacia or a poorly fitting tube
- Granulation tissue (most often at the site of the cuff or tip of the tube or at the anastomosis site of a transplanted lung or lobe)
- Dislodged tracheostomy tube (most common in obese patients in whom selection of the proper size and shape of the tracheostomy tube can be difficult)

bronchodilators or corticosteroids, or removal of granulation tissue. Until these measures are successful in alleviating intrinsic PEEP, however, an important step in achieving relief is to set the PEEP to equal the intrinsic PEEP (which reduces the preload the patient must overcome before triggering inspiration).[79] An alternative is to switch to mandatory volume-control ventilation, in which intrinsic PEEP does not affect delivery of tidal volume.

LOW COMPLIANCE

Stiffness of the respiratory system, as reflected by compliance (Crs) values less than about 40 mL/cm H_2O, is also a common cause of dyspnea. Common causes of low Crs are disorders involving the parenchyma (airspace diseases, fibrosis, and pulmonary edema), pleura (large pleural effusions, pleural thickening secondary to empyema, fibrosis, and tumor), or chest wall (kyphoscoliosis, ankylosing spondylitis, thoracoplasty, or obesity, especially in supine patients). These problems tend to be associated with a sense of effort to breathe, and with air hunger if hypoxemia or hypercapnia occurs. Many of the causes can be identified by chest computed tomography scan. Relief is obtained by reversal of the problem when possible.

FIGHTING THE VENTILATOR

Respiratory efforts out of phase with the ventilator often reduce its effectiveness by increasing effective impedance. These counterproductive efforts can be both an effect of dyspnea and resultant anxiety, and conversely, the efforts and consequent reduction in ventilation can be a cause of further dyspnea.

Dyspnea Associated with Care Activities

Dyspnea is frequently associated with normal care activities such as planned turns, transfers, bathing, and suctioning.[5] Good oxygenation should be assured before the activity, and it may be desirable to administer a preemptive dose of a very short-acting sedative or narcotic agent before commencing. A hazard of using even short-acting drugs repeatedly is that the drug will accumulate and produce prolonged sedation.

Ventilator Settings

Very few research papers have reported measures of dyspnea in patients during mechanical ventilation, and fewer still report the effect of systematic manipulations designed to reduce dyspnea. In most of these studies, respiratory discomfort was not the primary outcome measure, and ventilator settings were optimized according to the investigators' criteria, not according to subjects' reports of comfort.[40,41,80,81] A few studies in normal subjects and none in patients have systematically examined independent variables such as flow rate while holding other known stimuli for dyspnea constant. Usually several mechanoreceptor stimuli changed simultaneously; for instance, in one study when flow rate was changed, tidal volume also changed. In other cases, important physiologic variables secondary to ventilation were not controlled, and were often not even measured. For instance, although it is well known that Pa_{CO_2} and Pa_{O_2} have a powerful effect on air hunger, these variables are frequently not controlled or reported. Despite these limitations, it is clear from these studies that changing ventilator settings can reduce dyspnea, and that patients can report these changes in dyspnea—the two essential features to enable patient-centered ventilation. In an observational study of ninety-six patients mechanically ventilated of whom forty-five (47%) reported dyspnea, altering ventilator settings and/or increasing the level of ventilator support partially alleviated dyspnea in 35% of cases. This corresponded to a median reduction of reported dyspnea by 40% of full scale.[7]

LEVEL OF VENTILATOR SUPPORT

Major relief of dyspnea in ventilated patients can be obtained by increasing the level of ventilator support.[7] There is, however, very little systematic information on this phenomenon; we are aware of only one study in which ventilator variables, work of breathing, and dyspnea were measured at different levels of support by invasive ventilation.[41] This study of patients with chronic obstructive pulmonary disease presents data on respiratory sensation at graded levels of assistance. Increasing the percentage of respiratory work done each minute by the ventilator proportionally decreased ratings of "difficulty breathing" (Fig. 55-5). The effect was large, with breathing difficulty ratings falling from 60% of scale with no support to 30% of scale with 80% support (ratings were not

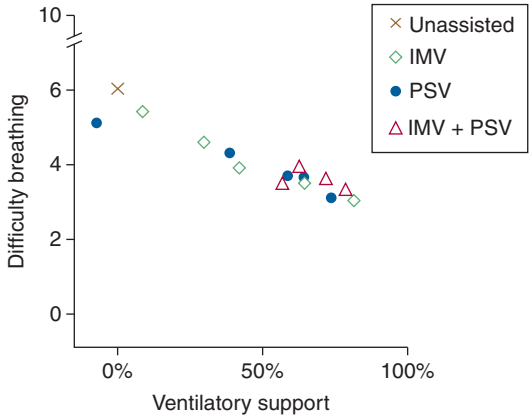

FIGURE 55-5 Effect of ventilator support on dyspnea. Subjects were instructed to rate "difficulty breathing" on a ten-point scale. Work of breathing was measured as the pressure-time product of inspiratory muscles, including all breaths, spontaneous and mandatory. Ventilator support is calculated as the difference from work of breathing in the unassisted control state. Data are shown for unassisted breathing, pressure-support ventilation (*PSV*), intermittent mandatory volume ventilation (*IMV*), and a combination of modes (*IMV+PSV*). (Data reanalyzed and redrawn from Leung et al.[41])

reported for full support). There were equally good correlations when ratings were replotted against a number of relevant physiologic indices (average tidal volume, frequency, minute ventilation, and work of breathing), so the afferent mechanism cannot be deduced from this experiment alone.

There are several mechanisms that could account for the relief achieved by increasing support. When support was increased in the above study, tidal volume also increased, as it would in most clinical situations. Relief correlated with tidal volume equally well as with percentage of support, and it is well known that increasing tidal volume can profoundly decrease air hunger (see the section above Effect of Lung Inflation on Air Hunger). Alveolar ventilation also increased with ventilator support in this study, presumably causing an improvement in blood gases, although these were not measured. Lowering Pa_{CO_2} has also been shown to have a profound effect on air hunger (see the section above Effect of Blood Gases on Air Hunger), providing another possible relief mechanism (not mutually exclusive).

OTHER ASPECTS OF VENTILATOR SETTINGS

Rate of inflation has been shown to have an effect on comfort. In healthy subjects on volume-control ventilation, inflation rates higher or lower than an optimum rate were less comfortable; there was, however, a broad range of comfortable inspiratory flow rates—the minimal comfortable flow, on average, was 0.6 L/s.[82] At inflation rates below the optimum, subjects reported air hunger. At inflation rates well above this minimal flow (average 1.8 L/s), subjects reported sensations of too much pressure. Optimal flow rate has also been shown in patients on pressure-support ventilation for conditions ranging from pneumonia to stroke; discomfort increased above and below the preferred setting.[40] In this latter study, however, there were concomitant changes in tidal volume that may have contributed to changes in discomfort ratings. Another study of ICU patients found a higher prevalence of dyspnea at inspiratory flow rates below 60 L/min (1 L/s), but concomitant changes in other key variables were not reported.[7] In a third study, a minimum inspiratory flow rate of 60 L/min was required to assure respiratory muscle relaxation in patients receiving assist-control ventilation.[83]

There is also evidence that PEEP level affects comfort via two distinctly different mechanisms: triggering effort and mean lung volume. The first, and best understood, arises from the interaction between ventilator PEEP and intrinsic PEEP in determining the effective trigger threshold. In this case, dyspnea can be reduced with little or no change in tidal volume by adjusting PEEP to minimize inspiratory muscle preload. The second effect is through the effect of lung volume on comfort. There is some evidence that chronic ventilator patients and mechanically ventilated healthy subjects are more comfortable (or require less tidal volume to achieve comfort) when end-expiratory lung volume is raised with PEEP,[84,85] possibly secondary to increased pulmonary mechanoreceptor activity.

EFFECT OF VENTILATOR CONTROL MODE

Most comparisons of sensation during different ventilator modes have not controlled the relevant physiologic variables. Leung et al[41] compared respiratory sensation during graded levels of support in two ventilator modes, pressure-support and intermittent mandatory ventilation, allowing meaningful comparisons of the two modes. The ratings of dyspnea ("difficulty breathing") depended only on the amount of assistance, not on the mode of ventilation (see Fig. 55-5). Both modes provided equivalent relief of dyspnea when ratings were replotted against a number of relevant physiologic indices. We conclude that judicious setting of volume-control ventilation parameters (see below) is likely to reduce dyspnea as effectively as subject-controlled ventilation when ventilatory demand is relatively constant.

A great deal of attention is paid to allowing patients to control the inspiration delivered by the ventilator; several clever schemes have been devised to perfect this control. It is thought by many that patient control of the ventilator is more comfortable, either because it ensures coincident timing of lung inflation with neural inspiration, or because it provides a sense of control to the patient. There is, however, no direct evidence that patient-triggered ventilation is inherently more comfortable than the same ventilator parameters set externally; differences appear to be more dependent on the parameter values chosen, and perhaps on the preference and familiarity of the operator for one mode versus another. There is growing evidence to show that use of the diaphragmatic electromyogram to initiate, control, and terminate pressure support (neurally adjusted ventilatory assist) improves patient–ventilator synchrony and allows more natural breathing variability.[86] The impact of neurally adjusted ventilatory assist on respiratory comfort, however, has not yet been determined.

If timing ventilator inflation to coincide with neural inspiration were crucial, spontaneous breathing in healthy subjects would be more comfortable than volume control; this is not the case. During hypercapnia in healthy subjects, spontaneous breathing was no more comfortable than volume-control mechanical ventilation at the same $\dot{V}_E$.[87] This may be because timing is irrelevant, or because neural timing adapts quickly to reasonable ventilator timing.[88,89]

If a psychological sense of control were important, giving the patient direct control of ventilator parameters would improve comfort; this is not the case, at least in chronically ventilated patients. When paralyzed patients on volume-control ventilation were allowed to control the tidal volume setting of the ventilator using a "sip/puff switch," they obtained no more relief from hypercapnia-induced discomfort than when the experimenter surreptitiously increased the volume.[90]

Patient-controlled ventilation may, however, have important advantages when ventilatory demand is highly variable. Two such instances are ambulatory patients assisted with noninvasive positive-pressure ventilation, whose ventilatory demand changes with physical activity,[80] and patients who use ventilator-delivered air to generate speech.

CHRONICALLY VENTILATOR-DEPENDENT PATIENTS

An illustrative case is that of the chronically ventilator-dependent neuromuscular patient. These patients are nearly always comfortable with their usual ventilator settings. The reason for this is that they are not sedated, and thus they clearly and insistently communicate their ventilatory desires to caregivers. In response, the caregivers set the ventilator to satisfy the patient. In our experience, this always results in high tidal volumes, frequencies of 10 to 15 breaths/min, and very low $P_{ET}CO_2$. In general, nearly all breaths are delivered by the ventilator as mandatory breaths, even when triggering is possible. Presumably this is because ventilation is high enough to suppress spontaneous efforts. Studies in which $P_{ET}CO_2$ is slowly raised show that complete comfort is maintained at normal $P_{ET}CO_2$, leading us to conclude that the factor suppressing dyspnea and spontaneous efforts is large tidal volume, rather than low P_{CO_2}. Patients with lung and heart disease present additional constraints that complicate the issue, but the general principle of obtaining feedback from the patient as part of the ventilator-setting process can probably be applied to most awake patients.

UNWANTED EFFECTS OF VENTILATOR ADJUSTMENTS

Ventilator-induced lung injury can be caused by overly high tidal volumes in vulnerable patients. It may not be necessary to give excessively high tidal volumes to achieve patient comfort. Although one observational study suggests that the tidal volume limit should be reduced in all patients, the study design limits the strength of the conclusions.[91] We also note that chronically ventilator-dependent neuromuscular patients are routinely maintained for years with much larger tidal volumes without experiencing ventilator-induced lung injury.[23,57,84,92] More restrictive limits should be observed in patients at risk for the acute respiratory distress syndrome, in which case other means must be used to avoid dyspnea. Clinicians should be sure to apprise themselves of the current state of the art for tidal volume limits, as this is a rapidly changing field. It seems particularly important not to extend attitudes and recommendations that have been developed for patients at high risk of lung injury to situations where their relevance is unknown. Exposing a patient to dyspnea and psychological trauma is not warranted if this patient is not at risk of acute lung injury.

Some clinicians become concerned if arterial P_{CO_2} falls below normal values. Again we note the experience of chronically ventilator-dependent neuromuscular patients, who invariably have arterial P_{CO_2} 10 to 20 torr lower than normal for many years without apparent ill effect.[57,83] It is important, however, to avoid acute increases in Pa_{CO_2} that give rise to dyspnea. Thus, for instance, if a patient is preparing to wean and is unlikely to have the ventilatory capacity to sustain low P_{CO_2}, the P_{CO_2} should be slowly raised over the course of a day or more to a level the patient is likely to be able to sustain with spontaneous breathing.

Sedation

It is commonly believed that heavy sedation is the best method to deal with patients who are uncomfortable during mechanical ventilation.[93,94] This is the usual approach in many hospitals. Mounting evidence suggests that this is a poor solution to the problem. It is intuitively evident that the loss of communication with loved ones and health care professionals is a serious disadvantage of sedation. It is also reasonably well established that heavy sedation worsens several outcome measures, such as length of ICU stay, length of hospital stay, and incidence of serious complications.[95] More recently, and more surprisingly, evidence has emerged suggesting that sedation worsens psychological outcome following discharge.[96,97]

Sedation may not eliminate discomfort even though it reduces outward signs of discomfort. What is known about the effect of sedation on pain suggests that some sedatives are ineffective in eliminating discomfort. For example, ratings of the discomfort of a controlled cutaneous pain stimulus were unaffected by propofol plasma concentrations up to 1.5 μg/mL (moderate sedation). Even at propofol concentrations that rendered subjects unresponsive, strong pain-related activations were seen in cortical regions associated with pain.[98,99] Although no similar studies exist for dyspnea stimuli, it is possible that cortical activation by dyspnea also persists during heavy sedation, providing a substrate for psychological trauma. It has been hypothesized that sedated patients can experience discomfort at some level, yet not have explicit recollections of stressful events.[100] They are therefore unable to construct a rational understanding of their discomfort, and are left with nightmarish recollection of the episode.[96,101]

Opioids are the only drugs recognized as effective in providing symptomatic relief of dyspnea. Relatively low doses of opioids can be effective. A recent meta-analysis showed a significant effect of opioids on clinical dyspnea, but the effect size was variable, probably because most of the included studies used oral dosing.[102] Parenteral doses are more consistently effective than oral doses.[103] In laboratory tests, morphine has been shown to specifically reduce air hunger,[103] the predominant symptom in ventilated patients.[7] Strom et al showed that it is possible to maintain ventilated patients with low doses of morphine and no other sedative; although no direct measurements of discomfort were reported, approximately 20% of patients required dedicated personal reassurance.[95] The duration of ventilation and ICU stay were shorter than in control patients sedated with propofol or midazolam.

COMFORT IMPLICATIONS OF THE PATIENT–VENTILATOR INTERFACE

Mechanical ventilation can be provided through a variety of patient–ventilator interfaces, including body tanks ("iron lungs"), endotracheal tubes, tracheostomy, masks, and helmets. It is customary to call support that does not involve tracheal cannulation as "noninvasive ventilation." Noninvasive ventilation is efficient as a life-support and symptomatic measure both during acute and chronic ventilatory failure. Noninvasive ventilation, when feasible, can

provide distinct advantages over endotracheal intubation for physical outcome,[104,105] and avoids major discomfort caused by the endotracheal tube.[106] Where conditions are suitable for noninvasive ventilation, it may even reduce posttraumatic stress disorder.[107] Patients supported by noninvasive ventilation, however, are not free from psychological trauma events.[18] It can be difficult to achieve both adequate gas exchange and comfort in the presence of leaks. Leaks promote patient–ventilator dyssynchrony[108] and may require the use of uncomfortable measures including high insufflation pressures and excessively tight application of masks.

Tracheotomy is probably the most ancient patient–ventilator interface. ICU mortality and morbidity are unaffected by tracheotomy;[109,110] although it has been associated with significant improvement of comfort in ventilated patients.[109,111] Tracheotomy can also allow spoken communication with caregivers and loved ones; more intubated patients are bothered by the inability to speak than by endotracheal tube discomfort,[112] although tracheotomy is often considered as very invasive by caregivers, patients, and relatives.

IMPORTANT UNKNOWNS AND THE FUTURE

Epidemiology

There are only a few small studies of the prevalence of dyspnea in mechanically ventilated patients. These pilot studies strongly suggest there is a reason for concern, but studies defining the extent of the problem and its variation in different categories of patients and in different care settings are needed. In addition, the connection between dyspnea in ICU patients and poor psychological outcomes needs to be more carefully studied. Having defined the extent of the problem, it will be necessary to study the effectiveness of patient-centered ventilation strategies on both immediate comfort and long-term medical and psychological outcomes.

Respiratory Interventions

Systematic studies of the effect of each of the multitude of ventilator setting modes on patient comfort are needed. These should be accomplished with state-of-the-art methods for dyspnea measurement, and with proper measurement and control of interrelated physiologic variables that may change. To date, there are no studies of ventilator settings that report measurements of discomfort together with measurements of the salient physiological variables that determine comfort (tidal volume, inspiratory time, frequency, blood gases, and so on). Further investigation is also needed to determine whether feedback on magnitude of discomfort will suffice as a practical guide to treatment of the mechanically ventilated patient, or whether obtaining further descriptions of the nature of discomfort will be useful.[13,69] On the basis of this mechanistic knowledge, a more systematic approach to achieving comfort can be devised.

Nonrespiratory Interventions

There are several potential schemes for altering afferent input without actually altering ventilatory variables, in a sense "fooling" the system to reduce perception of dyspnea. These have not been studied in the context of mechanical ventilation. Cool air directed over the face has a significant effect on dyspnea.[113] In some studies, phasic vibration of intercostal spaces has been shown to have an effect on work/effort dyspnea,[114–116] but no effect on air hunger.[117] Aerosolized furosemide has also been shown to reduce air hunger dyspnea.[118–120]

A complementary approach may be the provision of psychological support during the ICU stay. In one study, provision of a staff member to reassure and comfort those patients having difficulty with discomfort allowed lighter sedation. Such extra support was needed in only 20% of lightly sedated patients.[95]

SUMMARY AND CONCLUSION

Substantial respiratory discomfort is common in mechanically ventilated patients and is likely responsible for important emotional reactions, such as anxiety, fear, and PTSD. There is some irony in this, as mechanical ventilation is often instituted to relieve respiratory distress. Unfortunately, the current trend toward using low tidal volume ventilation in all patients exposes patients to dyspnea more often and for more prolonged periods. It will be of the utmost importance to explicitly recognize this trade-off, and to balance the clinical need for lung protection against the suffering that low tidal volume may engender.

Although it is not common current practice, we have recommended that, in ventilator units, there be routine formal assessment of the quality and intensity of the discomfort, for example, when vital signs are obtained. The cause(s) of the dyspnea should be sought and corrective measures attempted. The patient's description of the discomfort, the physical examination, and physiologic measurements, such as airways resistance and respiratory system compliance, provide important clues about the cause of the dyspnea. Increasing the level of mechanical support usually provides relief, but the best method for this is not yet known and may vary with the cause. Heavy sedation should be used only when necessary because it is associated with an increase in days requiring mechanical ventilation, occurrence of pneumonia, and length of stay in the hospital. Whether the patient-centered ventilation approach that we have recommended will yield beneficial outcomes remains to be determined and should be the subject of future research.

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